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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,903	02/06/2004	J. P. Devlin		8342

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,903	DEVLIN, J. P.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application claims benefit of provisional application 60/445717, filed February 7, 2003. Claims 1-6 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted July 1, 2004 is acknowledged wherein the claims and specification are amended to be in the proper format.

An examination of this application reveals that applicant is unfamiliar with US patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). In particular, the names of a number of registered practitioners are printed on the second page of the oath and crossed out without being properly initialed and dated.
>
> The full name of each inventor (family name and at least one given name together with any initial) has not been set forth. In particular, Applicant's full name is not **printed** under the heading, Given Name.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3 recite the phrase, "formula III" without providing any definition as to what is represented by formula III. Each claim must be self-contained. Additionally, claims 1-3 are drawn to an improvement. It is unclear to which statutory category, (i.e. a process, machine, manufacture, or composition of matter as described in 35 USC 101) the claims are directed and which specific prior art process, machine, manufacture, or composition of matter is being improved by the claimed invention. Claims 4-6 recite the identity of groups R1, R2, R3, R4, and R5, although these chemical groups appear nowhere else in the claims and do not clearly

denote any feature of the compounds used in the claimed invention. For these reasons, instant claims 1-3, and their dependant claims 4-6, are indefinite.

It is suggested that Applicant amend claims 1-3 to recite, "A method of treatment of _____" in place of the current wording, "in the treatment of _____ the improvement which."

Claims 4-6 recite the limitation "The method as recited in claim X" There is insufficient antecedent basis for this limitation in the claim. Claims 1-3 as presented are not clearly drawn to methods. Therefore claims 4-6 lack antecedent basis in the parent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Said claims appear to be drawn to therapeutic methods. However, Applicant's disclosure contains no descriptions of therapeutic methods for the treatment of inflammation, neurodegenerative diseases, or neoplastic diseases. No detains are given as to patient population, dosages or dosage forms, side

effects, prognosis, or other factors involved in a therapeutic method. The mere description of a compound and listing of its potential utilities does not adequately convey that one has possession of all possible methods of using said compound. Therefore Applicant's disclosure fails to provide adequate written description of the claimed invention to demonstrate to a skilled artisan in a relevant field that Applicant has possession of the claimed invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to improvements in the treatment of inflammatory, neurodegenerative, or neoplastic disease The improvement comprises administering to a warm-blooded animal a compound of formula III, where

formula III is described in the specification and includes dihydrocelastrol, dihydropristimerin, their diacetates and related compounds.

The state of the prior art: No methods of treating any disease by administering compounds of formula III are known in the prior art. The parent compound on which these compounds are based, celastrol, is known to possess unacceptable cellular toxicity which prevents it from being a useful pharmaceutical compound. The compounds used in the claimed methods are known to induce heat-shock proteins, which may make them therapeutically useful in the treatment of diseases involving these proteins. However, not enough is known about this effect to provide the basis for a useful therapy. In fact, it would appear that the known cytoprotective effects of heat-shock proteins may be counterproductive against neoplastic diseases. It is not generally taught in the art that the same treatment is effective for both neoplastic and neurodegenerative disorders, as the two categories of disease act in an opposite manner.

While the parent compound celastrol is a natural product component of a traditional Chinese remedy, the claimed invention is drawn to methods involving derivatives of this compound which are patentably distinct from celastrol. Therefore, the use of celastrol in traditional remedies for inflammatory conditions dose not enable one skilled in the art to practice a method of treating inflammatory conditions using the recited derivatives of celastrol having formula III.

It is speculated that the induction of heat-shock proteins by celastrol derivatives may provide the basis for treating Alzheimer's disease, prion diseases, and other

conditions associated with accumulation of misfolded proteins. However, this theory has not been tested *in vivo*. Furthermore, this therapeutic approach is only expected to be useful for the treatment of diseases associated with protein misfolding. Neurodegenerative diseases such as amyotrophic laterial sclerosis, which involve as yet unknown mechanisms of neurodegeneration, are unlikely to be treated by a therapy specifically targeting protein folding. Neurodegenerative diseases are a diverse collection of maladies which have not been demonstrated to share one single cause which could be targeted by a single agent. Furthermore, no neurodegenerative diseases have ever been successfully treated by a therapy aimed at elevating heat-shock proteins.

With regard to neoplastic diseases, celastrol is also known to possess cellular toxicity which hinders its therapeutic use. (p. 2, last paragraph) While cellular toxicity is often a desirable property in a chemotherapy agent, it must be directed specifically toward cancerous cells in order to be an acceptable therapy. Otherwise it is merely a poison which is not useful for selectively killing neoplastic cells.

Furthermore, the skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single chemotherapeutic drug is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs,

including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin. Breast cancer, on the other hand, is best treated with surgery and/or radiation, but the prognosis can be improved by the addition of adjuvant chemotherapy.

Thus the existing state of the art does not enable one skilled in the art to practice any therapeutic uses of compounds of formula III

The relative skill of those in the art: The relative skill in the art is high.

The predictability or unpredictability of the art: Neoplastic and neurodegenerative diseases are both broad categories encompassing numerous pathological conditions with diverse features. No one therapy is expected to be useful against all neoplastic diseases or all neurodegenerative diseases.

As mentioned above, no single treatment is effective for all cancers. Different cancers vary widely in their response to different chemotherapy regimens. According to the Oxford Textbook of Oncology, (Reference cited in PTO-892) "The important criteria for the tumor include its sensitivity to cytostatic drugs, its clinical stage and its mass, the presence of measurable lesions or biochemical markers, and, finally, growth characteristics," as well as, "*In vitro* sensitivity tests have been disappointing. They predict well for resistance but are of little use for sensitivity," (p. 451, right column, second paragraph) and, "For many types of cancer the potential benefit of chemotherapy has not been demonstrated in well-designed clinical trials."

Based on the known teachings of the prior art such as that stated above, one skilled in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors: gynecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CAN, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by performing the necessary experimentation to develop an optimized protocol for treating said cancers using compounds of formula III.

With regard to neurodegenerative diseases, there exists no agreed upon therapeutic target for treating all forms of neurodegeneration. While misfolded proteins have been suggested as a possible target for treatment of certain forms of neurodegeneration, this field has not been developed to the point where one skilled in the art could predict the effectiveness of such a therapeutic approach for all neurodegenerative diseases. Even for those diseases known to be associated with misfolded proteins, the claimed therapy will only be effective if the pharmacokinetic properties of the claimed compounds are such that they are delivered to the correct part of the body in the correct amounts for the correct duration, an assumption which has not been proven given the absence of any *in vivo* studies of the claimed compounds. This

is an especially important consideration given that the compounds are supposed to act by being converted into celastrol *in vivo*. (instant specification, p.3, last paragraph – p. 4, first paragraph)

Furthermore, administering a compound which has been shown to promote cell death under some circumstances may actually worsen the course of a neurodegenerative disease by promoting apoptosis. In the absence of *in vivo* data it is not possible to predict which effect will dominate under actual therapeutic conditions.

Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Additionally, the claims are interpreted to apply to new drugs for which comprehensive pharmacological data, such as optimal dosages and effectiveness against specific diseases, is not yet available.

The Breadth of the claims: The claims are drawn to the treatment of inflammatory, neurodegenerative, or neoplastic diseases by administering a compound of formula III. No specific conditions are mentioned, so the claims cover all inflammatory, neurodegenerative, or neoplastic diseases regardless of type or causes. For example, with regard to neoplastic diseases, the claimed invention is a method of treating any neoplastic condition without regard to which cell type it arises from, which tissue it occurs in, or which mutation triggered it.

The amount of direction or guidance presented: P. 1, under the heading, Background of the Invention, discloses that therapies targeting heat-shock proteins may

be useful against inflammatory, neurodegenerative, or neoplastic diseases. P. 2, lines 7-10 disclose that celastrol has been reported to induce apoptosis in a human leukemia cell line. However, celastrol is not a compound of the present invention. Its derivative, dihydrocelastrol, is reported to possess less cellular toxicity (and thus less potential antineoplastic activity) than its parent compound. (p. 2, last paragraph, p. 4, first paragraph) No guidance is given as to how these findings may be adapted into an effective therapeutic method.

Dihydrocelastrol, dihydropristimerin, and their diacetates are shown to induce elevated levels of heat-shock protein HSP70. (Table, p. 5) However, no context is given as to the conditions of this experiment, such as whether it was performed *in vitro* or *in vivo*, what cell types were used, how long the cells were incubated with the test compounds, or whether the increased HSP70 led to relevant biological effects such as cytoprotection against apoptosis or reduced deposition of amyloid plaques.

The presence or absence of working examples: There are no working examples in Applicant's disclosure of any therapeutic use for compounds of formula III. In particular, there are no working examples of its use for the treatment of inflammatory, neurodegenerative, or neoplastic disorders.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the treatment of neurodegenerative disease or cancer. See MPEP 2164.

The quantity of experimentation necessary: In order to use the disclosed information to practice the claimed invention for a wide range of diseases, a skilled

practitioner of the art would develop a specific therapeutic regimen for each condition. This would involve a process of optimizing and testing various regimens *in vivo* for each disease being treated. The skilled practitioner would start this process with no guidance from Applicant's disclosure as to the specific conditions expected to be treatable, the doses or dosage forms expected to be most effective, the frequency or duration of treatment, expected side effects, or any other details needed to devise an effective treatment regimen.

As the claimed compounds possess cellular toxicity, a study of their side effects would be undertaken before they could be reliably used for any therapeutic method. In addition to side effects stemming from cellular toxicity, side effects stemming from chronic up-regulation of heat-shock proteins would also be necessary, especially in the treatment of chronic neurodegenerative diseases, where a patient may be maintained on the therapy for the rest of their life in order to inhibit the progression of the disease. Determining the consequences of long-term therapy would require that the therapy be tested in a relatively long-lived animal model such as dogs, rather than in rodents which have too short of a lifespan to be useful for this purpose.

Furthermore, devising a therapeutic regimen for treating neurodegenerative diseases would involve the additional obstacle of finding suitable animal models. While certain conditions, such as prion diseases, are well studied in animals, no universally accepted animal model exists for Alzheimer's disease, for example. Thus experiments involving Alzheimer's disease would have to be repeated in several different model systems in order to reliably gauge the effectiveness of a particular therapy.

Still further, as neoplastic disorders are usually treated with combinations of drugs, the claimed methods would need to be modified to further take into account any positive or negative interactions with existing chemotherapy agents, necessitating yet more experimentation.

Therefore, given the absence of any guidance whatsoever from Applicant's disclosure beyond the mere suggestion that the disclosed compounds may be useful in therapeutic methods, one skilled in the art wishing to practice the claimed invention would be forced to undertake the development, from scratch, of many different therapeutic methods for many different and distinct diseases, many of which have never been treated successfully, using the same compounds as the active agent. This process would involve unpredictable experimentation which would constitute an undue experimental burden on the practitioner.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the lack of guidance or working examples in Applicant's disclosure, Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

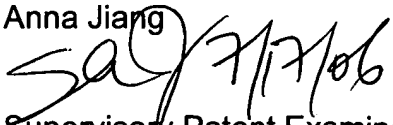
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson

Patent Examiner
AU 1623
7/11/06

Anna Jiang



Supervisory Patent Examiner
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